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THE CEREBROSPINAL FLUID

UNIV. OF CALIFORNIA

BY

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THE CEREBROSPINAL FLUID

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It is obviously impossible within the limitations of this review to present a truly comprehensive account of a characteristic body-fluid such as the cerebrospinal liquid. During the last century many contributions to our knowledge of this fluid have been made, though rather sporadically and with long intervals between publications. Anatomists, physiologists, pathologists and other workers have studied the problems of this fluid; the proper presentation of the many phases of the subject would lead into all of the representative biological sciences. But during the past two decades contributions of a physiological and anatomical nature have resulted in definite enlargement of our conceptions of this fluid which so completely fills the cerebral ventricles and surrounds the central nervous system. It is largely with these more recent advances in knowledge that this review will deal, taking from the older literature only those contributions which have founded the essential bases of the biological processes of the cerebrospinal fluid. It is purposed to omit in large measure the exact chemical, pathological and serological aspects of the subject except as the data from these investigations aid in establishing the fundamental anatomical and physiological phenomena which have to do with this fluid. For in this problem, as in many others, it has seemed obvious that the furtherance of investigations upon function has depended largely upon equivalent advance in anatomical knowledge.

The cerebrospinal fluid, as first effectively described by Magendie (48), is a clear limpid liquid of low specific gravity (1.004 to 1.006), colorless, and of a slight but definite viscosity. When withdrawn during life, the liquid usually contains but few cells per cubic millimeter (less than 10) but in many pathological conditions its cell-content may be enormously increased. Various estimates of the amount of the fluid existing in the cerebral ventricles and about the nervous system in adult man have been published; the computation of 100 to 150 grams

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given by Testut (65) is probably the most reliable, but because of the complexities of the fluid-bed the figures should necessarily be taken as an approximation.

Chemical examinations have demonstrated that the cerebrospinal fluid contains small quantities of inorganic salts, of protein and of dextrose. The inorganic salts are chiefly sodium chloride and potassium chloride; these occur in the ratio of 17.3 to 1, according to Mestrezat (50), whose monograph is a compendium of analyses of both normal and pathological fluids. The average pH value is given by Felton, Hussey and Bayne-Jones (27) as 7.75, with maximum variations of 7.4 and 7.9. Such chemical and physical characters induced Halliburton (37) to term the cerebrospinal fluid "an ideal physiological saline solution," bathing the neurones and maintaining their osmotic equilibrium.

This liquid, then, of distinctive constitution, unlike other body-fluids (except the aqueous humor of the eye) becomes the subject of review. Definite conceptions regarding its circulation are current, for the evidence today points to a constant production of the fluid, its passage through the cerebral ventricles and thence throughout the subarachnoid space, and its subsequent major absorption into the venous system. Necessarily, however, these conceptions must be subjected to critical analysis, to determine the character and reliability of the data supporting these viewpoints. For this purpose it becomes essential to arrive at some understanding of the anatomical mechanisms involved and to ascertain the functional employment of these structures as pathways for the cerebrospinal fluid. Such a discussion, while in no way comprehensively covering the problems of the cerebrospinal fluid, will present at least in part the phases of the subject which have in recent years been most extensively investigated.

THE SOURCES OF THE CEREBROSPINAL FLUID

The description of the glandular histological structure of the choroid plexuses by Faivre (25) in 1853 marked the discarding of the older concept of Haller and Magendie that the cerebrospinal fluid was a product of the leptomeninges (particularly of the pia mater). Faivre made the first histological survey of these villous projections, showing that the cell coverings were epithelial in nature and that there were indications of secretory activity in these cells. Faivre's observations, supported by similar histological descriptions of hyaline-like inclusions by Luschka (47) in 1855, gave origin to the hypothesis that the choroid plexuses elaborate the greater portion of the cerebrospinal fluid; this has remained

the hypothesis upon which most of the investigations regarding the source of this peculiar body-fluid have been based.

The purely histological evidence presented in support of this hypothesis, while suggestive, lacks the element of conclusive proof, though for many years accepted without question. During the past twenty years, however, renewed attempts with finer histological and cytological methods have been made to bridge the gap between intracellular secretion-granules (vacuoles) and the actual production of the liquid surrounding the cells. Thus, Findlay's (28) description of the granular structure of the normal epithelial cells of the plexus, with frequent inclusions of slightly pigmented globules representing the fusion of smaller elements and staining with osmic acid, is quite typical of the purely histological demonstration of secretion. Studnicka (64) obtained somewhat similar evidence of secretion by the cells of the plexus and by the ependymal cells of certain areas. Pettit and Girard (55) found hyaline-like globules, similar to those described by Luschka, in the cells of the plexuses in a comprehensive series of animals but did not feel that they represented secretion-vacuoles. Loeper (46), working on the plexuses in man, described pigmented granules and other granules within vacuoles staining with osmic acid; he stated that he believed that such histological findings permitted him to assert that the cells of the choroid plexuses are glandular. Employing methods of supravital staining in addition to the ordinary histological procedures, Schläpfer (61) concluded that the protoplasm of the cells of the choroid plexus contained "globoplasten" surrounded by a lipoid-like capsule; his histological findings offer but little additional support for his assertion that the choroid plexuses secrete the cerebrospinal fluid. Galeotti's (35) description in rabbit and mouse of three different intracellular inclusions (hyaline droplets, fuchsinophilic granules and small basophilic plasmosomes) afforded evidence of cell-activity by the choroidal epithelium but did not demonstrate the elaboration of the liquid by these structures. The same statement may be made of Francini's (32) differentiation of two forms of secretion-phenomena in these cells—droplets formed in the cytoplasm and granules derived from the cell-nucleus. Engel's (23) demonstration of a fuchsinophilic granule and a basophilic granule staining with methyl green is purely histological evidence of intracellular inclusions but the great variability in position of the granules can hardly be interpreted as indicating different phases in the secretion-process. And there is likewise no conclusive proof of function in Hworostuchin's (41) description of the changes in form of the mitochondria of the choroidal epithe-

lium as showing that the cells play an active rôle in the elaboration of cerebrospinal fluid. Yoshimura (80), in a histochemical investigation of the cells of the plexus, believed that the complicated process of secretion of the cerebrospinal fluid was related to the aggregation of the smaller cytoplasmic granules together into larger vacuoles for discharge. Pellizzi's (54) hypothesis that the epithelial cells of the plexuses secreted granules which increased in size by absorption of the fluid-plasm until extruded, was based on a comprehensive study of the plexuses in vertebrates and may likewise be considered as suggestive support of the general thesis.

It seems clear from the observations just detailed that while the many workers upon the histological structure of the choroid plexuses have described certain granules and vacuoles in these epithelial cells, there is no conclusive evidence that these intracellular structures constitute the intracellular mechanism for the elaboration of cerebrospinal fluid. The difficulty of final demonstration that these granules are discharged into the fluid or are in some way dissolved in that fluid, cannot at present be surmounted.

But fortunately observations of a far more conclusive nature have been made by a combination of pharmacological and histological methods. Cappelletti (9) reported in 1900 that ether and pilocarpine increased the flow of cerebrospinal fluid from an experimental fistula and that atropine and hyoscyamine diminished it. While considering that the differences in vascular reaction to these drugs might account for the phenomena observed, Cappelletti felt that the action of pilocarpine as a general stimulant of gland-activity justified the assumption that there was a true acceleration of secretion of the cerebrospinal fluid. Pettit and Girard (55) extended these observations of Cappelletti by introducing histological examinations of the choroid plexuses in animals which had been given muscarin, pilocarpine, ether, theobromine, etc. The administration of these substances was found to increase the volume of the cytoplasm of the choroidal epithelium, so that the cells became doubled in height. Histological study of these enlarged elements, both in the fresh and in fixed material, showed that the cells were divided into a densely granular basilar zone and a clear apical zone. While the clear apical area was indicated in the resting cell, the rapid enlargement of this zone, under the influence of muscarin, ether and theobromine, resulted in the formation of a distal clear vesicular mass. Such a demonstration of histological change in the choroidal epithelium under the influence of drugs which caused an increased flow of cerebrospinal

fluid from a fistula, was believed by Pettit and Girard to prove conclusively that the choroid plexuses possessed a secretory function in the elaboration of cerebrospinal fluid.

Meek (49), repeating the experiments of Pettit and Girard, came to identical conclusions. Muscarin caused no change in the choroidal epithelium in the rat but in the rabbit and guinea pig definite alterations were recorded. Meek stated (p. 300) that "the two things most striking about these modified cells are their great increase in height and the appearance of so much clear space at the distal side of the nucleus."

While the observations just quoted definitely relate the choroid plexuses to the elaboration of cerebrospinal fluid, there is available other substantiating evidence in support of this hypothesis. It had long been realized, from pathological examinations of cases of obstructive internal hydrocephalus, that the cerebrospinal fluid must be at least in part produced by some intraventricular structure. In this relationship renewed attention was directed to the choroid plexuses by the discovery by Claisse and Levy (12) in 1897 of a case of internal hydrocephalus associated with hypertrophy of these intraventricular plexuses. Dandy and Blackfan (17), (18) and Frazier and Peet (33) gave additional support to the general contention when they experimentally produced an internal hydrocephalus by occlusion of the aqueduct of Sylvius. Cushing's (14) observation of an exudation of a clear fluid from a choroid plexus exposed in exploration of a porencephalic defect likewise added suggestive substantiation of the hypothesis. Somewhat more tangible proof of intraventricular elaboration of the fluid was afforded by the writer's (68) demonstration that a definite and sustained outflow of cerebrospinal fluid could be obtained by catheterization of the third ventricle through the aqueduct of Sylvius. The outflow from such a catheter was quite similar in amount to the fluid obtained from a cannula in the subarachnoid space; the finding argues strongly for the belief that the major portion of the cerebrospinal fluid is produced within the cerebral ventricles. But Dandy's (16) later experiments constitute dependable evidence not only that the place of production of cerebrospinal fluid is intraventricular but that the choroid plexuses are the responsible structures. Dandy was able to produce a unilateral internal hydrocephalus by obstructing one foramen of Monro; extirpation of the choroid plexus in such an obstructed lateral cerebral ventricle prevented the development of an internal hydrocephalus. Dandy's experiment furnishes the strongest single substantiation of the hypothesis that the choroid plexuses elaborate the cerebrospinal fluid.

From an entirely different aspect, also, corroborative evidence in favor of the choroidal origin of the cerebrospinal fluid is found in embryological observations of the writer (69). In a study of the development of the cerebrospinal spaces it was shown that the first extraventricular expulsion of the cerebrospinal fluid occurred simultaneously with the first tufting and histological differentiation of the ependymal cells to form the choroid plexuses.

The evidence, then, from histological, pharmacological, pathological and embryological standpoints, surely inclines one to acceptance of the hypothesis that the choroid plexuses of the cerebral ventricles largely elaborate the cerebrospinal fluid. It does not seem justifiable to accept the evidence from any one standpoint as conclusive for many of the observations recorded are corroborative only. Yet the general histological structure of these plexuses, the cytoplasmic inclusions, and the modification of the cell-structure by pharmacological agents offer more than suggestive substantiation of the contention. The pathological studies of cases of internal hydrocephalus, the direct observations of the "sweating" choroid plexus, the embryological relationship between differentiation of choroid plexuses and extraventricular spread of the ventricular fluid, and particularly the experimental investigation of unilateral hydrocephalus, when considered as a whole, present a very strong argument, if not wholly conclusive, in favor of the view that the choroid plexuses are the elaborators of the major portion of the cerebrospinal fluid. It does not seem justifiable to discard, as Becht (1) has done, all of the evidence in favor of this hypothesis as inconclusive. While many of the experimental findings, when viewed as isolated observations, may be explained by other hypotheses, the great mass of data cannot be interpreted on any other hypothesis as satisfactorily. Certain of Becht's specific objections to acceptance of the theory of origin of the liquid from the choroid plexuses have been answered within the last year: Wislocki and Putnam (79) demonstrated by histological methods that in cases of experimental internal hydrocephalus there was absorption of foreign solutions through the ependymal cells lining the ventricles but not through the cells of the choroid plexus. These observations were confirmed and extended by Nañagas (53), who showed by similar procedures that an increased intraventricular absorption of fluid occurred after the intravenous injection of hypertonic solutions of sodium chloride; in no case was there absorption of the fluid by the cells of the choroid plexus. With this evidence in hand, it seems justifiable to disregard Becht's contention that the cell-changes in the choroid

plexuses, reported by Pettit and Girard and by Meek, may as properly be interpreted as indicative of absorption as of secretory activity.

But even as a working hypothesis, the choroid plexuses must not be considered to be the sole elaborators of the cerebrospinal fluid. Anatomical evidence presented by the writer (68) indicates that the perivascular spaces also pour a certain amount of fluid into the subarachnoid space, where this fluid mixes with the liquid produced in the cerebral ventricles. Such an addition to the cerebrospinal fluid probably accounts for the reported differences between subarachnoid and ventricular fluids on serological and chemical analysis. The ependymal cells lining the cerebral ventricles and the central canal of the spinal cord may also contribute even in the adult a minimal addition to the intraventricular cerebrospinal fluid.

Although a constant elaboration of cerebrospinal fluid by these mechanisms is indicated, it is not known how large a quantity is produced in any given time-interval but it is not unlikely that the majority of computations are by far too large. Most of the estimates in man have been based on the amount of fluid pouring from subarachnoid fistulae (also cases of cerebrospinal rhinorrhea) where the pressure, against which the fluid is produced, is determined solely by the resistance of the abnormal pathway. The same lack of normal conditions renders unreliable the determinations which are based on the rate of flow from experimental cannulae or fistulae. Estimations of the production of fluid based on the absorption of foreign dyes likewise may lead astray. The evidence indicates, however, that there is a constant though not excessive elaboration of the cerebrospinal fluid; the computations of exact quantities thus far given are of but little value.

CIRCULATION OF THE CEREBROSPINAL FLUID

The cerebrospinal fluid produced largely by the choroid plexuses is poured directly into the cerebral ventricles which are lined by ectodermal ependymal cells. That portion of the fluid formed in the lateral ventricles flows through the foramina of Monro into the third ventricle and thence by the aqueduct of Sylvius into the fourth ventricle. From the fourth ventricle the fluid passes out into the subarachnoid space; there is no evidence that functional communications between cerebral ventricles and subarachnoid space exist elsewhere than in this region.

The exact mode of escape of the ventricular cerebrospinal fluid from the fourth ventricle into the subarachnoid space must still be considered as slightly uncertain. It is possible that the inferior velum of the cere-

bellar roof in the adult is an intact though functioning membrane, as in the embryo; the existence of a perforation (the foramen of Magendie) in this membrane has been termed an artifact because of the dislocation of structures necessary to demonstrate it macroscopically or because of the shrinkage of tissues in embedding for histological investigation. The greater weight of evidence today inclines to a consideration of the foramen of Magendie as a true anatomical opening in the velum—a break in the ependyma and pia. In support of this conception of a true foramen between fourth ventricle and subarachnoid space may be quoted the observations of Cannieu (8) and of Wilder (78) and especially the developmental studies of Hess (38) and of Blake (6). Blake's conception of the formation of this opening—a shearing-off of the base of a finger-like evagination of the rhombic roof—is rendered more certain by recent morphological studies of this region. The two lateral foramina—those of Luschka—connecting the lateral recesses of the fourth ventricle with the subarachnoid space, seem to have as established a basis for their existence as does the medial. It is through these three foramina—or surely in the region of the inferior tela choroidea if through an intact membrane—that the cerebrospinal fluid, produced in the cerebral ventricles, passes into the subarachnoid space.

From the cisternal dilatation of the subarachnoid space in the region of the medial cerebello-bulbar angle the cerebrospinal fluid slowly seeps downward in the spinal subarachnoid space but passes more rapidly upward about the base of the brain and thence more slowly over the hemispheres, surrounding the whole central nervous system. This movement of fluid is facilitated by impulses transmitted to it by the vascular system; in the spinal region there is also an almost equivalent passage of fluid upward. The subarachnoid space, in which the fluid circulates, is, according to current anatomical descriptions, contained between the arachnoidea and the pia mater. Such a description does not present a proper conception of these fluid-containing channels, for it seems far preferable to consider the subarachnoid space to be intraleptomeningeal. On this basis the arachnoid may be described as the outer continuous membrane, intact and fluid-containing, from the inner surface of which project numerous delicate trabeculae, which merge with the pia mater. The surfaces of the arachnoid membrane and of the trabeculae are covered, as is the inner surface of the dura mater, by flattened, polygonal mesothelial cells. Identical cells also clothe the surface of the brain and spinal cord to form the essential cell-covering

of the pia mater. All structures (blood vessels, nerves, etc.) traversing the subarachnoid space are likewise covered by these mesothelial elements. The cerebrospinal fluid, hence, is contained within a completely cell-lined system of continuous yet partially interrupted spaces in the meshes of the arachnoid trabeculae. These meshes are of various sizes, increasing from very fine reticular spaces over the cerebral hemispheres to more widely calibered channels in the cerebral sulci and about the spinal cord, and reaching their maxima in the cisternal dilatations about the cerebello-bulbar angle. In the wide channels of this subarachnoid meshwork the cerebrospinal fluid is obstructed but little in its circulation, but in the small meshes the flow of the liquid is slowed.

Apart from their established function as efficient fluid-retainers, the cells lining the subarachnoid space are of great interest because of their changing morphology under different physiological conditions. The writer (70) first noted that these mesothelial cells phagocyted carbon granules introduced into the subarachnoid space and that when phagocytic, the cells increased in size. Essick (24) then showed that the presence of foreign material (laked blood, granules, etc.) caused these cells to become enlarged, vacuolated, phagocytic and finally detached to form free macrophages of the cerebrospinal fluid.

These mesothelial cells likewise have importance in establishing the relations between the subarachnoid and the perivascular spaces, for there is everywhere in the central nervous system a distinct fluid-containing space about each of the perforating blood vessels. The cells of the pia mater turn inward to form an outer wall of such a perivascular channel while the cells of the arachnoid, covering the vessel as it traverses the subarachnoid space, are likewise continued inward to form an inner cuff of this space. Thus each blood vessel penetrating the nervous system is surrounded by a cell-enclosed, peri-adventitial fluid-channel, which communicates directly with the subarachnoid space. The typical leptomeningeal mesothelial cell of this channel has been identified for variable distances from the surface, dependent upon the caliber of the penetrating vessel. The perivascular fluid-channel, when the mesothelial cell-cuff ceases, continues inward to connect directly with perineuronal spaces about the nerve-cells. These ultimate fluid-spaces are potential in character but under certain circumstances they become easily recognizable in microscopic preparations (Mott (52)). While originally termed "lymphatic" in character, these perivascular channels have no connection with the lymphatic system; they represent however an important accessory fluid-system of the cerebrospinal axis, affording direct

pathway, uninterrupted by cell-membranes, between nerve-cell and subarachnoid space.

Thus far mention of the dura mater has been omitted, for it has but slight relationship to the cerebrospinal fluid, the subdural space being anatomically and probably physiologically entirely apart from the subarachnoid. But in one respect the dura mater has importance in the present problem: the areas of penetration of the dense fibrous tissues of the dura by the arachnoid represent points of fusion between the two membranes. The most frequent of these areas of penetration are the arachnoid villi—prolongations of the arachnoid membrane so that the arachnoidal mesothelial cells come to be directly beneath the vascular endothelium of the great dural venous sinuses. Identified in adult man, in infants and in the common laboratory mammals (Weed (66), (67)), these villi are covered by typical arachnoid cells, usually of a single layer but often forming whorls and presenting double-layered coverings. The core of such a villus may be a strand-like network reduplicating the subarachnoid space or a myxomatous ground work simulating the perimedullary mesenchyme. In addition to the true arachnoid villi, which occur in the walls of practically all of the dural sinuses, there are found infrequently prolongations of the arachnoid into the dura in other situations. The arachnoid villi are normal structures; the great enlargement of these in adult life results in the formation of the well-known Pacchionian granulations.

The cerebrospinal fluid, then, circulates everywhere about the central nervous system—in the cerebral ventricles and central canal of the spinal cord and also in the tortuous meshes of the subarachnoid space. These channels are all clothed with a specialized cell, fluid-retaining so that a true circulation of fluid may be maintained. And in the arachnoid villi the circulating fluid comes into close relationship to the great venous sinuses of the dura mater.

ABSORPTION OF THE CEREBROSPINAL FLUID

With the evidence indicating a constant production of cerebrospinal fluid and a circulation of the liquid through the cerebral ventricles and throughout the subarachnoid space, it is not surprising that many investigations should have been undertaken to determine the mode of absorption of the fluid. The experiments performed fall naturally into two groups—the physiological observations to determine whether absorption of the fluid is into venous system or lymphatic trunks and the anatomical investigations to ascertain the exact pathways along which the fluid is

absorbed. Because of the great importance of this phase of the subject the evidence will be given in some detail.

Modern anatomical studies of the pathways of absorption of the cerebrospinal fluid were first made by Key and Retzius (43) who injected into the spinal subarachnoid space of a cadaver a gelatine solution colored with Berlin blue. While the pressure used was somewhat excessive (60 mm. Hg.), the anatomical continuity of spinal and cranial subarachnoid spaces was demonstrated, for the whole cranial subarachnoid space was filled with the gelatine-mass. Furthermore, the gelatine was traced into the core of the Pacchionian granulations along the great dural sinuses, and through the cell-membranes directly into these venous sinuses. Many beautiful plates showing this passage of the injection-mass but giving evidence of possible rupture are presented in Key and Retzius' monograph. In addition to this major pathway of absorption, these investigators demonstrated a minor accessory absorption of the fluid into the lymphatic system. Quincke's (56) confirmatory observations, though appearing before the monograph of Key and Retzius, did not antedate their earlier papers on the subject. Quincke injected into the subarachnoid space of living animals a suspension of cinnabar granules and, killing the animals at varying periods thereafter, discovered the granules almost wholly within the basilar and spinal subarachnoid spaces, for the most part held by phagocytic cells. Granules were also found along the venous sinuses in structures which he termed Pacchionian granulations; in the cervical lymph nodes likewise particles of the sulphide were identified.

For several years after these publications, the view of Key and Retzius was accepted as establishing the anatomical pathway of absorption of the cerebrospinal fluid. But gradually with the realization that Pacchionian granulations as such do not exist in infants and in the higher mammals, it was felt that this view was inadequate. For the next two decades practically no work was done upon the subject; then suddenly renewed interest in the problem was made manifest by the publication of several important physiological observations demonstrating a major absorption of the liquid into the venous system and a minor lymphatic drainage.

Reiner and Schnitzler (57) injected saline solutions containing potassium ferrocyanide into the spinal subarachnoid space of living animals and recovered the foreign salt in from 30 to 40 seconds from the blood of the jugular vein. Olive oil injected under similar conditions was identified likewise, though the blood stream was slowed. Reiner and

Schnitzler stated that as Pacchionian granulations do not exist in the animals used, other pathways of absorption must exist. Shortly thereafter Leonard Hill (39) reported that saline solution, colored with methylene blue and introduced into the subarachnoid space, could be traced "straight into the venous sinuses." Within a few minutes (10 to 20) after the injection, the blue was identified in the bladder and stomach; the cervical lymphatics became colored only after an interval of one hour. Following injection of potassium ferrocyanide into the cerebrospinal fluid, Ziegler (81) detected the foreign salt in the posterior facial vein in 10 seconds and only after 30 minutes in the cervical lymphatics. Similarly, Lewandowsky (44) identified sodium ferrocyanide in the urine of animals within 30 minutes after intraspinal introduction.

The experiments of Spina (63), though conducted under abnormally high pressures, likewise add support to the idea of a very rapid major venous absorption and a lesser lymphatic drainage. Cushing's (13) observations on mercury and non-absorbable gases led him to hypothesize a valve-like mechanism for drainage into the venous channel. Both of these observers commented upon the absence of Pacchionian granulations in the higher mammals.

Mott (52) in 1910, from study of the brains of animals subjected to experimental cerebral anemia, suggested a new pathway for the absorption of the cerebrospinal fluid, based on the occurrence of distinct spaces about each nerve-cell, connected through the perivascular channels with the subarachnoid space. Believing that this fluid-system contained cerebrospinal fluid, Mott contended that normally the liquid passes from subarachnoid space into cerebral capillaries. Cathelin (10), without supporting data, assumed that the major absorption of the cerebrospinal fluid was into the lymphatic system; and Goldmann (36), employing subarachnoid injections of trypan blue, likewise tentatively favored this view, though acknowledging the weight of evidence in favor of the major venous drainage.

Dandy and Blackfan (17) in 1913 concluded that the absorption of cerebrospinal fluid was a "diffuse process from the entire subarachnoid space," for with the spinal subarachnoid space isolated from the cranial, they found "a quantitative absorption proportionately as great as from the entire subarachnoid space." The evidence for these statements (18), published in detail a year later, was largely based on the excretion by the kidneys of a readily diffusible dye—phenolsulphonephthalein—after its introduction into the subarachnoid space. A very rapid

absorption into the blood stream occurred under such experimental conditions while the lymphatic drainage was minimal in amount and very tardy. After subarachnoid injections of india ink, Dandy and Blackfan were able to find no anatomical evidence of absorption of the carbon granules—an observation in accord with those of Quincke (56) and of Sicard and Cestan (62).

It was with these contributions as a background that the writer (66), (67), (68) began his anatomical studies of the absorption of the cerebrospinal fluid. Critical examination of the preceding work was convincing in demonstrating a major venous absorption and a minor lymphatic drainage of the liquid, but the reliable data were practically entirely physiological. Thus the observations regarding the rapid venous absorption of readily diffusible substances seemed wholly dependable but the anatomical evidence was satisfactory solely in demonstrating that insoluble particles (cinnabar, carbon) did not leave the subarachnoid space in any great amount. The only complete morphological investigations were those of Key and Retzius; these were unsatisfactory because the injections were performed on dead material, the pressures employed were high (60 mm. Hg.) and the injection-mass was a viscous colloid (gelatine) colored with Berlin blue. It was felt that the experimental approach must be such that a subarachnoid injection of a true, isotonic solution of non-toxic foreign salts, capable of subsequent precipitation in situ for histological examination and not diffusely staining cellular material, could be made in the living animal, under pressures not greatly in excess of the normal. With these criteria established, experiments were undertaken with subarachnoid injection of potassium ferrocyanide and iron-ammonium citrate in isotonic solution under pressures but slightly above the normal (130–180 mm. H_2O). Subsequently the central nervous system, enclosed in meninges, was fixed in an acid medium; precipitation of the foreign salts as Prussian blue permitted adequate histological identification of the pathway taken. This method was found to meet all of the standards of investigation set.

The experiments were carried out over periods of several hours in living anesthetized animals, with introduction of the isotonic foreign solution into the lumbar subarachnoid space. The spinal and basilar portions of the subarachnoid space were rapidly filled with the foreign solution but the cerebral portion of the space was not completely injected until the experiment had been continued for several hours. Histological examination demonstrated that the solution had not pene-

trated any of the cells lining the subarachnoid space; the precipitated granules adhered to the surfaces of the cells but were not within the cytoplasm. The foreign solution was found to have passed directly into the venous sinuses by way of the arachnoid villi into which the precipitated granules could be traced from the cerebral subarachnoid space. These granules, representing the foreign solution, were found within the mesothelial cells covering the villi and the endothelial cells lining the venous sinuses, as well as within the lumen of the venous sinus, thus demonstrating the essential pathway of absorption. In no other place was there evidence of direct passage through a cell-membrane as in the villi. The mechanism of passage of this fluid seemed to be a process of filtration from a point of higher pressure (subarachnoid space) to a point of lower pressure (venous sinus), though the factors of osmosis and diffusion were not excluded. The absorption of true solutions from the cranial subarachnoid space was shown to be a much more efficient and rapid process than was the corresponding absorption from the spinal subarachnoid space. Suspensions of particulate matter were found, in agreement with the observations already recorded, to be retained within the meshes of the subarachnoid space.

In addition to this major venous absorption through arachnoid villi directly into the great dural sinuses, an accessory drainage by way of the lymphatic system was demonstrated. This seemed a much slower, less efficient means of absorption of the fluid, caring for but a small fraction of the total. Such lymphatic absorption was wholly indirect; the fluid reached the true lymphatic vessel only outside of the dura and then by way of perineural spaces.

These anatomical findings, based on a standard of experimentation which approximated the normal, agreed largely with those of Key and Retzius, substituting however for the Pacchionian granulation the normal arachnoid villus. Further observations were made to ascertain the truth of the other anatomical hypotheses ventured for the absorption of cerebrospinal fluid: thus, no structure of a valve-like nature was found in many examinations of serial sections of the great dural sinuses. Mott's theory of absorption by cerebral capillaries was excluded by the failure of the injection-fluid to pass into the perivascular system under conditions approaching the physiological. Dandy and Blackfan's conception of a diffuse absorption by the vessels of the subarachnoid space was likewise found untenable, for in no case were the mesothelial cells covering these vessels penetrated by the foreign solution. The strongest argument in favor of the diffuse process of absorption advanced by

Dandy and Blackfan was that the excretion of phenolsulphonephthalein from the isolated spinal subarachnoid space was proportionately as great as from the whole cranial and spinal subarachnoid space. The technique employed by Dandy and Blackfan involved withdrawal of an equivalent amount of cerebrospinal fluid from the isolated spinal subarachnoid space before injection of 1 cc. of the phenolsulphonephthalein solution. The writer (67) believed that this substitution could not be made in this isolated space without increase in the spinal subarachnoid pressure and escape of the foreign dye into the epidural tissues. By reversing the experiment he was able to show that absorption of phenolsulphonephthalein when introduced into the cisterna magna was as rapid when the spinal subarachnoid space was excluded as with the whole cranial and spinal subarachnoid space functioning. The cranial portion of the nervous system seems, therefore, to contain the efficient mechanisms for the absorption of cerebrospinal fluid.

Since the publication of this work in 1914 there have been other observations regarding the absorption of the cerebrospinal fluid; all accord with this idea of a major venous absorption of the fluid. Thus Frazier and Peet's (33) experiments with methylene blue, isamine blue, trypan red, trypan blue and phenolsulphonephthalein demonstrated the greater importance of the rapid venous absorption and the lesser of the slow lymphatic drainage. And Dixon and Halliburton (21), in the course of their studies of the cerebrospinal fluid, confirmed this general conception of the process, finding no escape of particulate matter from the subarachnoid space but a free and rapid absorption of true solutions. Between the two types there occurred a much slower absorption of colloidal solutions than of true solutions, the larger molecules being absorbed more slowly than the smaller. They concluded, as did also Halliburton (37) that "the fluid probably reached the venous sinuses by way of the microscopic arachnoid villi." And recently the writer, in work as yet unpublished, has repeated certain phases of his original investigation of the pathways of absorption, with continuous observations of the pressures of the cerebrospinal fluid and of the intracranial blood vessels. The results confirm in every way the conception of the mechanism here presented.

Thus it seems fair to assume that the absorption of the cerebrospinal fluid is a twofold process, being chiefly a rapid drainage into the great dural sinuses, and in small part a slow indirect escape into the true lymphatic vessels.

THE PRESSURE OF THE CEREBROSPINAL FLUID

Practically all of the methods of recording the pressure of the cerebrospinal fluid deal with connection of the subarachnoid space to an open or membrane manometer. It is very difficult with any of the procedures to avoid the loss of a few drops of fluid, but by immediate replacement of this liquid and by the use of manometers filled to the estimated level of the fluid, the pressures obtained by these simple methods may be accepted as accurate.

Very few, if any, of the early records of the pressure of the cerebrospinal fluid were sufficiently controlled to permit direct comparison with the data obtained by recent workers. As examples of the variation in the pressures recorded by the earlier investigators, the following determinations may be given: Key and Retzius (43), 162 to 216 mm. H_2O in inspiration and 216 to 270 mm. H_2O in expiration, in etherized dogs; Bergmann (4, 5), 80 mm. H_2O in his first observations and in his second series, 120 to 160 mm. of salt solution in narcotized dogs; Falkenheim and Naunyn (26), 100 to 150 mm. H_2O in curarized dogs; and Leyden (45), 80 to 150 mm. and 100 to 120 mm. H_2O in dogs under morphia. Leonard Hill (39) believed, however, that the intracranial tension might vary from zero to 50 mm. Hg. and that the variations reported by the earlier observers were but expressions of this characteristic of the intracranial pressure.[1] Hill's idea of variability in the normal pressure of the cerebrospinal fluid seemed supported by the observations of Dixon and Halliburton (20), who reported 40 to 70 mm. of salt solution as a rough average of the normal pressures obtained in the dog under morphine-urethane anesthesia. And in a single detailed protocol presented, the pressures at 5-minute intervals ranged as follows: 95, 25, 30, 35, 55, 25, 80, 65, 65, 65, 75, 70, 60, 55, 50, 80, 90 mm. of 10 per cent citrate solution.

The most recent work, particularly by American investigators, has given much better knowledge of the range and variability of the normal pressure of the cerebrospinal fluid. Weed and McKibben (75) reported an initial average of 119 mm. of Ringer's solution in cats anesthetized by intratracheal ether, and an extreme constancy of the pressure of the cerebrospinal fluid under such experimental conditions. Becht (1) found considerable fluctuation in the pressure of the fluid in etherized dogs but of lesser extent than did Dixon and Halliburton; his average

[1] Within the limits of the physiological phenomena investigated, intracranial pressure may be considered to be identical with that of the cerebrospinal fluid.

pressure of 112 mm. (sodium chloride solution of specific gravity of 1.088) was derived from 39 dogs under intratracheal ether. Foley and Putnam (31) presented a slightly higher average of 127 mm. for the normal reading in animals under ether while the average of 100 animals under various anesthetics was 133 mm. of cerebrospinal fluid; no comment upon the extent of normal fluctuations of the fluid pressure was made. And recently Weed and Hughson (72) have reported an average pressure of 119 mm. of Ringer's solution for 77 cats under ether by Woulfe bottle; the fluctuations in the pressure under the experimental conditions were very slight in extent (11 mm. in an animal under observation for 2 hours).

The question of greatest physiological interest in this phase of the general problem is that of the maintenance of this pressure of the cerebrospinal fluid. All of the conceptions of the mechanism for the maintenance of this pressure are based primarily upon the rigid character of the bony coverings of the nervous system. This idea that the cerebrospinal axis is situated within a "closed box," to which the physical laws of such a system apply, was first advanced in 1783 by Alexander Monro (51). Monro believed that the substance of the brain, like that of other solids of the body, is nearly incompressible and is "enclosed in a case of bone," assuring therefore the constancy of the intracranial blood content. The development of this hypothesis by Kellie (42) in 1824 led to wide acceptance, and the Monro-Kellie doctrine with but few alterations has served as the basis upon which the physiology of the intracranial contents has been interpreted. The doctrine was modified by the introduction of the cerebrospinal fluid into the consideration by Burrows (7) under the influence of Magendie's epochal studies; the hypothesis was then formulated by Burrows as follows (p. 32): "the whole contents of the cranium, the brain, the blood and this serum (cerebrospinal fluid) together, must be at all times nearly a constant quantity."

Many physiologists have subjected this Monro-Kelllie doctrine to experimental proof not only in dead but in living animals; while divergent conclusions have been arrived at, the general consensus of opinion expressed in the literature of the last century has been in favor of the hypothesis. And in the hands of recent workers a similar unanimity of expression holds though occasional investigators express doubt as to the accuracy of the premise. Lately, Weed and Hughson (73) have experimentally demonstrated the essential truth of the doctrine that (p. 99) "the bony coverings of the central nervous system constitute

within tested physiological limits, inelastic and rigid containers; the ordinary physical laws of a 'closed box' may therefore be applied to the cranium." And with appreciation of the variability in volume of the constituents, the hypothesis may be stated, as was done by Weed and McKibben (76, p. 553): "the cranial cavity is relatively fixed in volume and is completely filled by brain, cerebrospinal fluid and blood; variations in any one of the three elements may occur, compensation being afforded by alteration in the volume of one or both of the remaining elements."

With the cranium and vertebral column serving as rigid containers, the relation of the intracranial vascular pressures to the pressure of the cerebrospinal fluid requires immediate consideration. Current physiological conceptions of these intracranial mechanisms really date from the work of Leonard Hill (39) who advanced the idea that intracranial pressure is (p. 71) "the same as cerebral venous pressure, and varies in the same direction absolutely as general venous pressure, and proportionately as general arterial pressure." Hill's technical procedures consisted in determing cerebral venous pressure in the torcular Herophili and cerebrospinal fluid pressure in the occipital region.

The emphasis placed by Hill upon this equality of pressure dominated physiological opinion for over fifteen years; it was not until the publication of Dixon and Halliburton (20) in 1914 that contradictory evidence was presented. Using experimental procedures essentially similar to those of Hill, Dixon and Halliburton demonstrated that the cerebrospinal fluid pressure is not identical with that of the dural venous sinus, and stated that the fluid pressure is (p. 153) "influenced passively to a small extent by changes in the arterial and venous pressures but such alterations are insignificant compared with the independent changes in pressure which occur as the result of secretory activity." These investigators also showed that increase in the cerebrospinal fluid pressure produced a passive increase in the cerebral venous pressure but not of the same extent; conversely, alteration of the cerebral venous tension caused similar though not identical alteration in the pressure of the cerebrospinal fluid. Under normal conditions the arterial pressure was found by Dixon and Halliburton to be higher than the intracranial venous pressure which in turn was always higher than that of the cerebrospinal fluid.

Becht (1), employing somewhat similar methods, came to conclusions in some respects at variance with those of Dixon and Halliburton though confirming the general contention of inequality of cerebrospinal fluid

pressure and cerebral venous pressure. Becht stated that the cerebrospinal fluid pressure was dependent upon both intracranial arterial and venous pressures, though not identical with either. The data obtained indicated that either the cerebral venous (torcular) or cerebrospinal fluid pressure might be the higher but that usually the former exceeded the latter. Passive changes in the torcular pressure were found to affect the pressure of the cerebrospinal fluid, in the same direction but not to the same extent; but within fairly wide limits changes of the cerebrospinal fluid pressure were not believed to alter the pressure of the torcular.

The observations of these recent workers were all carried out with fairly similar technical procedures, particularly for the determination of venous pressure in the torcular Herophili. The very wide divergences in these normal pressures (13 to 601 mm. in Becht's series) indicate that the method is subject to many experimental defects. Weed and Hughson (74), with these technical disadvantages in mind, devised a simple method for recording intracranial venous pressure in the superior sagittal sinus as it empties into the torcular. The procedure possessed the very distinct advantage of permitting direct observations of the effect of the manipulative procedure upon the pressure of the cerebrospinal fluid, thus affording control of artificial increases in the pressure of the cerebrospinal fluid due to venous obstruction in the cranium. With such technical controls, Weed and Hughson were able to show that in practically every case the pressure of the cerebrospinal fluid was considerably above (5–50 mm.) that of the sagittal sinus. They also presented data which indicated, in accordance with the findings of Dixon and Halliburton and of Becht, that alteration in intracranial venous pressure effected alterations in the pressure of the cerebrospinal fluid in the same direction but of lesser magnitude. Conversely it was shown, in agreement with Dixon and Halliburton, that within the physiological limits tested, alteration in the pressure of the cerebrospinal fluid caused changes of lesser extent but of the same direction in the sagittal venous pressure.

This conception, advanced by Weed and Hughson, that the pressure of the cerebrospinal fluid is practically always above that of the cerebral veins, alone affords basis of explanation for Wegefarth's experiments. Wegefarth (77) demonstrated that an experimental communication between subarachnoid space and superior sagittal sinus remained patent, without hemorrhage into the meningeal cavities, for at least 4 days. Removal of cerebrospinal fluid in these animals, however, resulted in

immediate intrameningeal hemorrhage. Such an observation, free from the errors of recording instruments, can be explained only on the basis that normally the pressure of the fluid is above that in the sinus or that the former is constantly being reduced toward the latter.

Analysis of the reliable data concerning these normal relationships seems convincing in demonstrating that the pressure of the cerebrospinal fluid practically always exceeds that of the superior sagittal sinus. In no sense may the two pressures be regarded as identical, for such an identity of pressures is found only in animals in which the technical procedures have resulted in the production of direct communications between sinus and meningeal spaces. In the normal animal intracranial arterial pressure is a factor of importance in the maintenance of the pressure of the cerebrospinal fluid, though slight or slowly effected changes in this arterial tension have but little influence upon the fluid pressure. Thus while dependent upon both intracranial arterial and venous pressures and while influenced passively and in the same direction by both, the pressure of the cerebrospinal fluid may be considered to be relatively independent of both in that normally it maintains an individual, fairly constant level far below that of the intracranial arteries and somewhat above that of the intracranial veins.

It becomes desirable, then, to ascertain the factors which determine the level of the cerebrospinal fluid pressure, but in this inquiry there are practically no data available and the problem becomes speculative. Yet it is instructive to think of the cerebrospinal fluid as being largely elaborated by the cells of the choroid plexuses where the pressure in the blood capillaries is estimated at from 40 to 60 mm. Hg. On the outer side of these cells is the cerebrospinal fluid with its pressure of 110 to 130 mm. of Ringer's solution. After circulating through the cerebral ventricles and subarachnoid space this fluid is largely returned into the venous sinuses of the dura where the pressure (as determined in the superior sagittal sinus) is below that of the cerebrospinal fluid (as determined in the cisterna magna). On such a basis the normal mechanism for the absorption of this characteristic body liquid may well be a simple process of filtration though the factors of osmosis and diffusion are not excluded in the passage of the fluid through the cell-membrane of the arachnoid villus. No determinations of the pressure of the cerebrospinal fluid in the arachnoid villus have been made but it is unlikely that this pressure is markedly different from that of the cisterna magna. Obstruction to any part of the pathway of the fluid results in raising intraventricular tension (cf. Nañagas (53)) thus demonstrating that

cerebrospinal fluid can be produced against higher pressures than normally exist in the cerebral ventricles. The normal pressure therefore may be largely determined by the balance between the constant new production within the cerebral ventricles and the absorption into the dural sinuses: this pressure of the cerebrospinal fluid becomes dependent also upon intracranial arterial and venous pressures, not only because of the relation of these latter pressures to the production and absorption of the fluid, but because of the constancy of volume of the intracranial contents.

MODIFICATION OF THE PRESSURE OF THE CEREBROSPINAL FLUID

During the past ten years a number of investigators has studied the alterations in pressure of the cerebrospinal fluid effected by the introduction of various substances into the blood stream or alimentary canal. The subject-matter naturally differentiates itself from the purely mechanical modifications effected by pressure-changes in the cerebral blood vessels. The general findings in this latter group of experiments have been presented in the foregoing section of this review; the pressure-changes effected in the cerebrospinal fluid by solutions of various concentrations and by certain pharmacological agents and tissue extracts will be discussed here.

Solutions of various concentrations. In 1919 Weed and McKibben (75) reported that the pressure of the cerebrospinal fluid could be markedly altered by the intravenous injection of solutions of various concentrations. It was shown that such administration of strongly hypertonic solutions lowered the pressure of this liquid to an extreme degree, frequently producing negative values; with hypotonic solutions (distilled water) a prolonged rise in the pressure of the fluid was obtained. Ringer's solution in large doses produced a temporary increase in the pressure of the cerebrospinal fluid, followed quickly by a return to normal levels. Accompanying these changes in fluid pressure, Weed and McKibben (76) found marked alterations in the volume of the brain, the hypertonic solution producing a small shrunken brain while the hypotonic solution caused an outspoken swelling of the brain-substance. The experimental changes in brain volume were particularly pronounced in animals in which the cranial cavity had been opened by trephining.

These physiological findings have since been abundantly confirmed and clinical applications of the phenomena have been developed. Cushing and Foley (15) demonstrated that similar alterations in the

pressure of the cerebrospinal fluid could be brought about by the ingestion of hypertonic and hypotonic solutions. Subsequently Foley and Putnam (31), after verifying the original conclusions, studied similar changes in the pressure of the cerebrospinal fluid which were effected by the intra-intestinal administration of these solutions of various concentrations. And Sachs and Malone (60) reported observations upon the decrease of brain volume caused by the intravenous injection of strongly hypertonic solutions. In addition to these papers, there has appeared a number of reports of clinical application of this experimental modification of fluid pressure or brain bulk—notably those of Cushing and Foley (15), Sachs and Belcher (59), Ebaugh and Stevenson (22), Foley (30) and Hughson (40).

Recently Weed and Hughson (72), (74) have extended the original observations of Weed and McKibben (75); in addition to confirming the initial work in detail, they have presented data showing the general systemic and intracranial vascular alterations effected by these agents. These observations were made over periods of from 2 to 7 hours, under adequate experimental conditions in which the pressures recorded (cerebrospinal fluid, carotid artery, superior sagittal sinus, superficial brachial vein) remained surprisingly constant. The intravenous injection of a large quantity of Ringer's solution was shown to cause a temporary rise in the pressure of the cerebrospinal fluid with increases in both sagittal and brachial venous pressures, the former being the greater. At the end of the injection-period all of these pressures tended to return to their previous levels, normal pressures customarily being attained within 30 minutes. After the intravenous injection of distilled water in similar amount, a prolonged rise in the pressure of the cerebrospinal fluid occurred, accompanied by alterations in both sagittal and brachial pressures. Both of these venous pressures increased during the period of injection and for a few minutes thereafter, the sagittal outstripping the brachial; within 30 minutes these pressures were usually returned to their pre-injection levels, though the pressure of the cerebrospinal fluid was still elevated. With the intravenous injection of strongly hypertonic solutions, the pressure-alterations were most striking, the cerebrospinal fluid, after a frequently occurring rise during the interval of injection, dropping markedly and often exhibiting extreme negative values. The pressure in the superficial brachial vein rose during the period of the hypertonic injection and then rapidly resumed its pre-injection level or a new level slightly below. More significant were the alterations in sagittal venous pressure: here the reaction during the

period of injection depended largely on the reaction of the pressure of the cerebrospinal fluid, but following this the sagittal pressure was always lowered to a greater extent than was the brachial venous pressure.

These experiments afforded a unique opportunity for study of the mechanisms which normally control the pressure of the cerebrospinal fluid. Analysis of the data demonstrated that alterations in the pressure of the cerebrospinal fluid could be effected and maintained independently of change in the intracranial and systemic vascular pressures. The most striking similarities in reactions were those between the pressure of the cerebrospinal fluid and that of the brachial vein and sagittal sinus; after the injection of Ringer's solution or of distilled water they exhibited somewhat the same alterations, differing not only in magnitude but in duration. After the intravenous injection of hypertonic solutions, however, the relationships of the pressures were markedly altered, with the pressure of the cerebrospinal fluid profoundly lowered, the sagittal venous considerably and the brachial venous but little if at all. Both brachial and sagittal venous pressures were found to be lower than the pressure of the cerebrospinal fluid in the control-periods; this relationship held after the injection of isotonic and hypotonic solutions but was reversed when hypertonic solutions were given. Arterial changes, when slowly brought about, caused little if any alteration in the pressure of the cerebrospinal fluid, but when abrupt, their influence was marked.

The changes in the pressure of the cerebrospinal fluid, effected by the intravenous injection of solutions of various concentrations, must in the final analysis find their explanation in the alteration of the osmotic pressure of the circulating blood. The injection of a large volume of an isotonic solution was followed by a short-enduring rise of the cerebrospinal fluid pressure which subsided in approximately the same time-interval required for the pressure-changes effected by the hypertonic and hypotonic solutions to reach their maxima. The usual time for maximal reaction of the pressure of the cerebrospinal fluid was noted to be from 25 to 35 minutes after the end of the intravenous injection; in this interval the organism was attempting to compensate for alteration in the volume and salt-content of the blood. With the isotonic solutions, the compensation was one for increased volume of fluid only; this compensation, if judged by the time of return of the cerebrospinal fluid pressure to normal, was rapidly achieved. When, however, not only the volume of the circulating blood was increased but its salt-content relatively diminished as by the intravenous injection of distilled

water, two processes of adjustment proceeded. The blood tended to reëstablish its normal salt-content by passage of water into the tissues and possibly into some of the body-fluids, and by attraction of salts from these places; and it also tended to compensate further by alteration of the vascular bed. The increase in the pressure of the cerebrospinal fluid and in the brain volume may be taken to be a rough index of the passage of fluid from blood vessel to tissue; the return of the vascular pressures to normal levels while the pressure of the cerebrospinal fluid remained high, indicated the completion of certain of the phases of readjustment. In the readjustments effected by the organism to the injection of hypertonic solutions, there were somewhat similar phases, yet differing because the great increase of fluid-volume in the circulating blood was not immediate but was due to the attraction of water from the body-tissues and possibly from the body-fluids—a phenomenon shown by the decrease in brain volume and by the reduction of the pressure of the cerebrospinal fluid.

Such an explanation of the phenomena reported leads one naturally to a consideration of the rôle played by the osmotic pressure of the blood in the normal process of absorption of the cerebrospinal fluid. And intimately connected with such a problem is that of the volume of the brain in its relation to the intracranial pressure. At the present time there are available no data which will permit of exact statement; it must be realized that the osmotic changes in the blood, effected by such relatively large injections of solutions of various concentrations, are probably beyond the ordinary physiological limits of change. But if one may judge merely by the anatomical and physiological evidence afforded by subarachnoid injection of isotonic foreign solutions, osmosis and diffusion play subordinate rôles in the normal process of absorption of the cerebrospinal fluid into the blood stream.

Pharmacological agents and tissue extracts. Most of the work done on this subject has been actuated by the tenet that alteration in the pressure of the cerebrospinal fluid, without significant change in intracranial vascular pressures, affords a more reliable means of determining the effect of these various agents upon the rate of production of the fluid than the outflow method. While logically this subject should perhaps be discussed under the heading of the modification of the rate of elaboration of the liquid, it may properly be treated here as an experimental alteration of the fluid pressure.

It may be stated at the outset that there is no unanimity of opinion regarding the effect of either pharmacological agents or tissue extracts

upon the pressure of the cerebrospinal fluid, without significant alteration in intracranial arterial or venous pressures. Dixon and Halliburton (20) found that extracts of the choroid plexus, chloroform, ether, urethane, carbon dioxide, amyl nitrite, pilocarpine and other drugs caused a "secretory rise" in cerebrospinal fluid pressure which was independent of the intracranial vascular alterations. Becht (1) has investigated the subject from the same angle, using methods somewhat similar, and has stated that (p. 124) "all the changes in the fluid pressure and in the fluid outflow which have been offered as proof of the secretory mechanism of formation of the cerebrospinal fluids can be traced to alterations in venous and arterial pressures in the skull." Similar conclusions have been reached by Becht and Matill (3) and by Becht and Gunnar (2).

With this conflicting evidence it is of course impossible to do other than reserve opinion in the matter. But certain aspects of the controversy may be commented upon. Dixon and Halliburton and Becht determined cerebral venous pressures in the torcular Herophili—a method which because of the wide divergences in normal pressures reported does not seem adequate though qualitative changes in the pressures are probably fairly accurately shown. While the simple manometric method has been modified by Becht and Gunnar (2), it still has certain limitations in determining a true change in rate of production of cerebrospinal fluid. Of these, the fact that the normal channels of absorption are intact and functioning is the most obvious though Becht has minimized the weight of this objection. There is however a much more formidable disadvantage in that the manometric method cannot take into account the experimental alteration of the volume of the brain. The pressure-changes in the cerebrospinal fluid, effected by the intravenous injection of distilled water, appear to fulfil, after the period of acute vascular change, all of the conditions necessary for the determination that the injection has caused an increased production of fluid—a markedly elevated cerebrospinal fluid pressure with intracranial vascular pressures at the pre-injection levels. The outspoken increase in brain volume under such conditions, however, may well be the sole explanation of the phenomenon; until the experimental variations in brain volume are more fully understood, the evidence obtained by the manometric method should be accepted only with reservations.

MODIFICATION OF RATE OF OUTFLOW OF CEREBROSPINAL FLUID

That certain pharmacological substances may modify the rate of flow of cerebrospinal fluid from a cannula introduced into the subarachnoid space was first determined by Cappelletti (9) in 1900. Employing Cavazzani's (11) method of making a fistula into the cistern region, Cappelletti showed that ether given by intratracheal tube in a curarized dog increased the rate of flow of the fluid from 0.15 to 0.35 grams per 15-minute interval to 4.72 grams for the same interval. A second, a third and a fourth administration gave momentary increases but not of the same extent as the initial. Similar positive results were obtained with pilocarpine, but the increases though obvious were not marked. Very slight augmentation of the rate of outflow was also obtained with amyl nitrite, while atropine and hyoscyamine caused a decrease and on repetition a cessation of the outflow.

Pettit and Girard (55) immediately confirmed and extended these experimental findings of Cappelletti, including in their studies histological examination of the choroid plexuses. And Meek's (49) observations were likewise entirely confirmatory. The scope of the investigation was widened in 1913 by Dixon and Halliburton (19) who studied the effect of a large number of substances upon the rate of outflow of cerebrospinal fluid from an occipito-atlantoid cannula. They were able to classify the substances into four groups according to their effect on this rate of outflow, placing the volatile anesthetics, alcohol, carbon dioxide and extracts of choroid plexus and of brain in the group which caused marked increase in secretion. Slight increases in the outflow were found to be caused by large injections of water or of normal saline, cholesterin, kephalin, atropine, pilocarpine and amyl nitrite. In the large third group of substances which caused no increase or a diminution of secretion were included extracts of the pituitary, of mussel, of pineal and of pia mater, glucose, urea, lecithin, etc., while in the last group where the effect was possibly masked by vascular or respiratory changes, were muscarin, pilocarpine, adrenalin, etc.

Shortly thereafter Dandy and Blackfan (18), obtaining cerebrospinal fluid by introduction of a special cannula through the atlas, found marked accelerations of the rate of output of cerebrospinal fluid following administration of ether and slight augmentations after pilocarpine. With amyl nitrite and extracts of choroid plexus and of posterior lobe of the hypophysis, no change in the rate of output of the fluid was observed.

Realizing the limitations of this technique in that the normal channels of absorption were intact and that the intracranial pressure was reduced to the resistance of the needle, Weed and Cushing (71) in 1915 catheterized the third ventricle and studied the outflow from the catheter whose resistance was established at approximately normal pressure of the fluid. In addition, cerebrospinal fluid was obtained by callosal and occipito-atlantoid punctures with needles of similarly standardized resistances. Under these circumstances the intravenous injection of extract of posterior lobe of the hypophysis was found to increase the outflow of cerebrospinal fluid. This finding was explained by Dixon and Halliburton (21) on the basis that the hypophysial extract had caused a contraction of the bronchioles and consequent asphyxia. Dixon and Halliburton used an intermittent blast for their artificial respiration while Weed and Cushing employed intratracheal insufflation: it seems questionable whether this explanation of the finding will suffice.

At this time also, Frazier and Peet (34) reported that brain-extract increased the secretion of the cerebrospinal fluid as determined by outflow and that thyroid extract decreased it, independently of any vascular changes.

The later studies of the effect of these substances upon the rate of production of cerebrospinal fluid have been made by the manometric method and have been discussed in the preceding section of this review. The limitations of the outflow method were realized by Weed and Cushing (71) in 1915; their modifications introduced control for some of the sources of error but were incomplete. As Becht (1) has pointed out, practically all of this work is of no scientific value because of failures to record simultaneously the intracranial arterial and venous pressures. Using this standard but employing the manometric method, Becht and Matill (3) have concluded that there is no indisputable evidence that the tissue extracts tested have a specific action on the cerebrospinal fluid. And recently Becht and Gunnar (2) reported that adrenalin, pituitrin, pilocarpine and atropine did not increase the production of cerebrospinal fluid, as determined by manometer readings. It is true that the method of recording the rate of outflow of cerebrospinal fluid from a cistern cannula, even with careful determinations of intracranial vascular pressures, yields unreliable data, but in many ways, also, the manometric method fails. Both of these methods, which at the present time are the only technical approaches to the problem, are of questionable value because they both fail to take account of the experimental variation in brain-bulk. When a method which will permit of actual

determination of this variable brain bulk, with observations also of cerebrospinal fluid pressure and with a record of intracranial vascular pressures, is devised, data of conclusive value will be obtained. And yet one cannot but lay stress upon the changes in the choroidal epithelium recorded by Pettit and Girard (55) after the injection of pilocarpine. Likewise, as first reported by Cappelletti (9) and since noted by many workers, the rapidly decreasing responses to ether and pilocarpine suggest strongly that the accelerations of flow of cerebrospinal fluid under these conditions were not due solely to vascular alteration, for such ready fatigability would not seem to be associated with a vasomotor reaction.

In this connection it is interesting to speculate upon the possibility of modification of the rate of elaboration of the cerebrospinal fluid, after the intravenous injection of solutions of various concentrations. There is as yet no evidence of value in this regard, though Foley and Putnam presented data which suggested that after the injection of a strongly hypertonic solution, a new ratio between the rate of production and absorption of the cerebrospinal fluid became established. But the final elucidation of this phase of the problem will require additional work before definite conceptions are acquired.

RELATIONSHIP OF CEREBROSPINAL FLUID TO NERVOUS SYSTEM

Many phases of the relationship existing between the central nervous system and the cerebrospinal fluid are of utmost significance in the present discussion. Filling the cerebral ventricles and central canal of the spinal cord, the fluid also completely surrounds the cerebrospinal axis in the subarachnoid space. This double relationship has prompted many observers to look upon the cerebrospinal fluid as constituting a fluid-cushion for the central nervous system within the closed system of cranium and vertebral column. It has also prompted other workers to liken the cerebrospinal fluid to the lymph of the nervous system—a conception which in the light of present knowledge of the lymphatic system is untenable.

Halliburton (37), in a recent lecture, declared that the cerebrospinal fluid serves as the lymph of the brain, though clearly differentiating it from the true lymph of the lymphatic vessels. It seems likely that such a designation, even when correctly qualified as Halliburton has stated it, is apt to introduce error. All modern investigators of the lymphatic system are agreed that true lymphatic vessels do not exist within the dura mater; the older descriptions of such lymphatic vessels were actu-

ally descriptions of intradural tissue-channels, subpial tissue-channels, or arachnoidal cell-columns within the dura mater. As Sabin (58) has pointed out, our knowledge of the lymphatic system has advanced so that it becomes now necessary to restrict the term "lymph" to the fluid contained within true lymphatic vessels and not to use it to designate any body-fluid.

But in one respect the cerebrospinal fluid does function as an accessory fluid to the central nervous system. In foregoing sections the drainage of the fluid contained within the perivascular channels toward the subarachnoid space has been commented upon; this fluid really becomes added to the ventricular cerebrospinal fluid in the subarachnoid space. In that sense, then, these perivascular spaces represent accessory drainage channels, uninterrupted by cell-membranes and capable of carrying toward the subarachnoid space the waste products of nerve-cell activity. Lacking a true lymphatic system, the nervous tissue apparently makes use of these perivascular channels as pathways for fluid elimination.

The ultimate connection of these perivascular channels with potential spaces about each nerve-cell indicate the close relationship between the cerebrospinal fluid and the nervous system. And in addition to these rather obvious fluid spaces about the nerve-cells, there is evidence indicating that this fluid-system is intimately connected with the general tissue-channels through the ground-substance of the brain. The general direction of flow of this fluid under normal conditions seems to be toward the subarachnoid space.

But under certain conditions this direction of flow may be reversed so that the cerebrospinal fluid passes from subarachnoid space to nerve-cell. The first of these conditions is that of cerebral anemia in which, as Mott (52) showed by histological study, all of the perivascular, pericapillary and perineuronal spaces are dilated. The author (68) made use of this phenomenon as a means of injecting this perivascular system from the subarachnoid space. The second of these conditions under which the perivascular flow is toward nerve-cell, is brought about by the intravenous injection of strongly hypertonic solutions. This phenomenon was first noted by Weed and McKibben (76) who supplied a foreign solution of sodium ferrocyanide and iron-ammonium citrate to the subarachnoid space at the time when the cerebrospinal fluid pressure was approaching zero, following the intravenous injection of a strongly hypertonic solution. This foreign solution was subsequently found (p. 536) "to have passed from the subarachnoid space along the

perivasculars into the substance of the nervous system, reaching the interfibrous spaces in the white matter and the pericellular spaces in the gray." These observations were interpreted as indicating that, under the influence of the intravenous injection of the strongly hypertonic solution, the dislocation of a considerable quantity of cerebrospinal fluid into the nervous system occurred.

Foley (29) has subsequently carried out experiments quite similar to those reported by Weed and McKibben, using the same foreign salts for subarachnoid introduction and intravenous injections of strongly hypertonic solutions. In addition to the findings already detailed, Foley obtained evidence of a retrograde absorption not only by ependyma but by choroid plexuses. The absorption by the ependyma is amply verified by the work of Wislocki and Putnam (79) and Nañagas (53), but these latter workers, using careful histological control, have been unable to obtain evidence of absorption of the foreign salts by the choroid plexuses.

And in work as yet unpublished the writer has repeated many of his earlier experiments done with McKibben, with findings confirmatory in every regard. The intracranial vascular and the cerebrospinal fluid pressures have been determined both before and throughout the period of subarachnoid introduction of the foreign solution, so that definite physiological control is afforded. The results indicate that with the increase of osmotic pressure of the blood, due to the intravenous injection of hypertonic solutions, the cerebrospinal fluid is aspirated into the shrinking nervous system, chiefly along the perivascular channels but also through the ependymal lining of the ventricles. Along these channels, under this extraordinary osmotic pull, actual absorption of the fluid into the vessels of the nervous tissue takes place. The findings suggest a reversal, following the injection of the hypertonic solution, of the normal processes; the osmotic pressure of the blood stream, under these conditions, seems to be a determining factor in the absorption of the cerebrospinal fluid. Interpretation of certain of the experimental observations makes it seem likely that diffusion also plays a part in the process.

RÉSUMÉ

The limitations of this review have made it impossible to more than rather briefly discuss a few of the many problems connected with the cerebrospinal fluid. Many equally absorbing phases have been untouched for one or another reason but an attempt has been made to

indicate the type of evidence which has furnished the working hypotheses and to point out the limitations of the procedures on which so many conclusions have been based.

Our present knowledge of the processes of the cerebrospinal fluid in many respects is inadequate. The conception that this characteristic body-fluid is largely produced by the intraventricular choroid plexuses is based not on any single conclusive piece of evidence but on a mass of suggestive data; when considered from all standpoints, however, the hypothesis seems today well established. The current ideas regarding the circulation of the fluid through cerebral ventricles and subarachnoid space are founded largely on exact anatomical evidence, particularly in regard to the structure of the meninges and the use of these intrameningeal channels as fluid-pathways. And likewise, there are firm and reliable data of an anatomical and physiological nature supporting the contention that the cerebrospinal fluid is absorbed largely into the venous system and to a lesser extent into the lymphatic channels. It is possible now to discard the hypothesis of equality between the cerebrospinal fluid pressure and that of the cerebral veins, and to regard the cerebrospinal fluid as being maintained at an individual, relatively independent pressure at fairly constant levels above that of the sagittal venous sinus. The conceptions of pressure-changes effected by the intravenous injection of solutions of various concentrations are substantiated by dependable observations, but it does not seem as yet justifiable to accept, without further control, the data furnished in regard to similar changes brought about by administration of pharmacological agents and tissue extracts. And the same cautions may be urged in regard to the acceptance of conclusions based on the effects of various agents upon the rate of outflow of the fluid.

Yet these problems are but few of the many fascinating subjects of investigation in this field. The interesting questions of the chemical composition of the fluid have not been discussed: is the cerebrospinal fluid a true secretion, a transudate, or a modified dialysate? Likewise, the long-debated problems of the passage of foreign salts, of drugs, etc., from blood stream into the fluid must be left for future review, though with possibly a note of suggestion that these investigations be carried out with control of the cerebrospinal fluid pressure. And so may the many other partially answered questions centering about this fluid be enumerated.

But in this field of research the work of the next few years will solve certain problems; yet the solution of these will but expose wider fields

for examination. Here, as in countless other investigations, the study of structure must proceed hand in hand with the study of function, for many of the erroneous conceptions introduced into the literature of the cerebrospinal fluid have been due to failure to give regard to one or other of these basic factors. Future investigations will be the more profitable if the studies be largely along the lines of physiological-anatomical control.

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